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Isovolumic Relaxation Period in Hypertrophic Cardiomyopathy

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Previous reports have demonstrated that patients with hypertrophic cardiomyopathy have a prolonged isovolumic relaxation period as a result of a delay in mitral valve opening, reflecting a reduced rate of fall of left ventricular pressure. This period as measured from the aortic closure sound (A_2 on phonocardiogram) to the opening of the mitral valve (on echocardiogram) was determined in 84 patients with hypertrophic cardiomyopathy and compared with findings in 31 normal volunteers. The duration of the isovolumic relaxation period in the 84 patients had a wide range from 0 to 160 ms (mean 71 ± 32) that was not significantly different from that in normal subjects (63 ± 11 ms). However, it was possible to identify a group of 15 patients with an extremely short isovolumic relaxation period, 2 standard deviations below the normal range. This shortening was due to a marked delay in aortic closure sound (A_2) due to late left ventricular-aortic pressure crossover, as well as early opening of the mitral valve secondary to elevated left atrial pressure, which was confirmed by hemodynamic correlations and digitized echocardiographic data. In this subset of patients, A_2 is a poor marker of the onset of rapid left ventricular pressure decline and, thus, the interval from A_2 to mitral valve opening is not a valid reflection of left ventricular relaxation.

It is concluded that in hypertrophic cardiomyopathy, both the timing and sequence of relaxation are abnormal, as is the rate of relaxation. Furthermore, the isovolumic relaxation period is multifactorially determined and depends not only on the rate of left ventricular pressure decline, but also on the magnitude of the pressure drop from A_2 to mitral valve opening. All of these determinants must be kept in mind when the isovolumic relaxation period is used as a measure of left ventricular relaxation.

Recent reports (1–12) have demonstrated significant abnormalities of diastolic function in patients having hypertrophic cardiomyopathy These abnormalities have been present with or without a left ventricular outflow pressure gradient and are found in the setting of massive myocardial hypertrophy, which involves the interventricular septum and also the ventricular free wall to varying degrees A number of noninvasive indexes of left ventricular relaxation have been used to evaluate diastolic function and all have shown impaired relaxation manifested by an increase in the duration of left ventricular pressure decline The noninvasive index used in earlier studies (13,15) showed a prolongation of the interval from aortic closure to the O point of the apexcardiogram More recently, studies have shown prolongation of the interval from minimal dimension of the left ventricular echocardiogram to the opening of the mitral valve (2,5–7), as well as prolongation of the isovolumic relaxation period as measured from the aortic component of the second heart sound to the opening of the mitral valve (7,10)

We recorded all of these noninvasive indexes of diastolic relaxation in a comprehensive study of 70 patients with hypertrophic cardiomyopathy evaluated at the Hammersmith Hospital, London (7) and 14 additional patients studied at the Health Center Hospitals of the University of Pittsburgh The diastolic time intervals of these 84 patients with documented hypertrophic cardiomyopathy were compared with those obtained in 31 normal subjects Although the majority of these patients had prolongation of these noninvasive indexes consistent with previous reports, there were 15 patients with marked abbreviation of the isovolumic relaxation period greater than 2 standard deviation below the normal range All of these patients had classic clinical and echocardiographic findings of severe hypertrophy with a significant left ventricular outflow gradient documented during hemodynamic study

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It is the purpose of our study to report the spectrum of the diastolic time intervals found in this large group of patients with hypertrophic cardiomyopathy, to elucidate the mechanism of the short isovolumic relaxation period found in some patients and to analyze the validity of the isovolumic relaxation period as a measure of diastolic relaxation in patients with hypertrophic cardiomyopathy

Methods

Study group. Eighty-four patients who fulfilled the clinical (16), echocardiographic (17–19) and hemodynamic-angiographic (20,21) criteria for hypertrophic cardiomyopathy were studied (Table 1) Their ages ranged from 11 to 73 years (mean 43 ± 16) Fifty-three were male and 31 were female Their mean heart rate was 70 ± 14 beats/min and 74 had normal sinus rhythm, 9 had atrial fibrillation and 1 had pacemaker rhythm None of these patients had taken any drug for at least 1 week and none had either a history or the presence of high blood pressure Thirty-one normal subjects served as the control group They had no symptoms or signs of cardiovascular, renal or pulmonary disease Their ages ranged from 22 to 38 years (mean 30), 25 were male and 6 were female

Noninvasive recordings. These 84 patients and 31 normal volunteers were studied with simultaneous recordings of the phonocardiogram, apexcardiogram, left ventricular and mitral valve echocardiogram and electrocardiogram (Fig 1) All recordings were made on an Electronics for Medicine VR-12 recorder at a paper speed of 100 mm/s and time lines indicating 20 ms This afforded optimal measurement of diastolic time intervals with an accuracy of ± 4 ms (22)

The apexcardiogram and phonocardiogram were obtained using an Electronics for Medicine model PSA-23 crystal transducer with a time constant greater than 3 seconds With the patient lying comfortably in the left lateral recumbent position, the transducer was positioned at the point of maximal cardiac impulse and held in place by an adjustable elastic strap The model V-2207 phonocardiographic amplifier then permitted selective display of the apexcardiogram with a frequency response of 0 1 to 30 Hz and a phonocardiogram with a frequency range from 50 to 1,000 Hz When necessary to clearly define the aortic component of the second heart sound, an additional microphone was placed at the base and the carotid pulse was also recorded.

A simultaneous echocardiogram was obtained, using the Electronics for Medicine model V-3280 module and a 1 25 cm diameter, 2.25 MHz transducer (Transducer Manufacturing Services) This system provides a pulse repetition rate of 1,000 cycles/s and multilevel gain compensation in either continuous time mode or discrete depth mode with independent adjustments every 2 0 cm over a 24 cm range The transducer was directed so that the ultrasonic beam passed through the left ventricular cavity at the level of the tips of the mitral leaflets Echoes were obtained simultaneously from interventricular septum, posterior wall and both leaflets of the mitral valve, with special attention given to the point where the anterior and posterior leaflets separate In a few cases, when it was not possible to record all of these anatomic structures simultaneously with one transducer position, sequential tracings were recorded by repositioning the tranducer to give optimal display of each structure for subsequent analysis During each examination, gauge settings were continuously adjusted until the best available records could be obtained

In each study, the ultrasonic beam was also directed toward the aortic root where the aortic valve and posterior wall of the left atrium were recorded simultaneously with the carotid pulse and phonocardiogram (Fig 2) The carotid pulse was recorded with a 231-D Gould Statham pressure transducer coupled to the skin overlying the carotid artery by an air-filled tube and cone The sharply inscribed incisura was used to accurately define the aortic component of the second heart sound

Calculation of diastolic intervals. From these recordings, the following diastolic intervals were calculated from a minimum of five consecutive cardiac cycles (Fig 1)

A_2-MO Interval from the first high frequency vibration of the aortic component of the second heart sound (A_2) to the mitral valve opening (MO) defined as the point where both leaflets of the mitral valve separate on the echocardiogram This interval represents the period of isovolumic relaxation

A_2-O Interval from the first high frequency vibration of A_2 to the O point of the apexcardiogram

MO-O Interval from the opening of the mitral valve to the O point of the apexcardiogram This interval represents a period of rapid ventricular filling while ventricular pressure is decreasing. Its duration is determined by the dynamic interplay between the rate of filling versus the rate of relaxation

Digitized data. In 70 of the patients with hypertrophic cardiomyopathy and in 11 normal subjects these simultaneous tracings were digitized as previously described, echoes were traced from the left side of the septum and the endocardial surface of the posterior wall, anterior and posterior leaflets of the mitral valve and from the apexcardiogram using a Summagraphics digitizing table interfaced with a Prime 300 computer (23,24) Single points of physiologic interest were identified, including the first high frequency vibration of the aortic component of the second heart sound, the time of the mitral valve opening and the O point of the apexcardiogram (Fig 3)

The echoes were calibrated with points defining a time interval of 500 ms, 1 cm depth and two successive R waves on the electrocardiogram enclosing the cardiac cycle to be analyzed. From the digitized data, plots were made of the position of the septum, posterior wall and mitral valve echoes

Table 1. Data in 84 Patients

Case	Age (yr)	Sex	Rhythm	Heart Rate	Main Symptoms		Duration (yr) of Symptoms	Pressure Gradient		SAM	Reversed Splitting	Midsystolic Closure	A_2-MO (ms)	A_2-O (ms)	MO-O (ms)
					Angina	Dyspnea		At Rest	On Provocation						
1	60	M	SR	56	–	+	24	+	+	+	–	+	100	220	120
2	36	M	SR	81	+	+	12	+	+	?	–	?	160	240	80
3	42	M	SR	74	–	+	10	–	–	–	–	–	90	180	90
4	32	M	SR	58	–	+	7	–	+	–	–	–	45	130	85
5	48	M	SR	61	+	–	16	–	–	–	–	–	85	275	190
6	32	F	SR	53	+	+	10	–	–	–	–	–	85	190	105
7	41	M	SR	72	+	–	10	–	–	–	–	–	110	245	135
8	37	M	SR	63	+	+	10	+	+	–	–	–	95	215	120
9	38	F	SR	69	+	+	11	+	+	+	–	+	60	180	120
10	46	F	SR	48	+	+	22	–	+	+	–	+	100	175	75
11	—	M	SR	77	?	?	?	0	0	–	–	?	70	160	90
12	46	M	SR	65	–	+	4	–	+	+	–	+	60	175	115
13	44	M	SR	66	–	+	0	–	–	–	–	–	100	160	60
14	43	M	SR	66	+	–	28	–	–	–	–	–	110	220	110
15	51	M	AF	86	–	+	5	–	–	+	–	+	45	115	70
16	30	M	AF	79	+	+	15	–	+	–	–	–	70	140	70
17	58	F	AF	84	–	+	25	–	+	–	–	–	90	145	55
18	57	M	AF	130	–	+	7	–	+	–	–	–	60	135	75
19	57	M	AF	110	+	–	15	–	–	+	–	+	75	155	80
20	44	M	AF	83	+	+	11	+	+	–	–	–	90	170	80
21	14	M	SR	76	–	+	3	–	–	+	–	+	60	125	65
22	48	M	SR	67	+	+	4	+	+	–	–	–	55	130	75
23	38	F	SR	69	+	+	18	–	+	–	–	–	75	175	100
24	31	F	SR	74	–	+	15	–	+	+	–	+	75	150	75
25	34	M	SR	55	–	–	5	–	+	+	–	+	60	170	110
26	57	M	SR	73	–	+	14	–	+	+	+	+	45	150	105
27	17	M	SR	70	–	–	0	–	+	+	–	+	105	270	165
28	63	F	SR	71	–	+	15	–	–	–	–	–	90	190	100
29	56	F	SR	77	–	+	10	–	+	+	–	+	125	215	90
30	—	M	SR	75	?	?	?	0	0	+	–	–	50	120	70
31	58	M	SR	56	–	–	5	–	–	–	–	–	125	170	45
32	44	M	SR	61	–	+	4	–	+	–	–	–	115	215	100
33	59	F	SR	48	–	+	13	–	+	–	–	–	105	145	40
34	47	M	AF	71	–	+	5	+	+	+	–	+	60	140	80
35	44	M	SR	56	+	+	8	–	+	+	–	+	55	145	90
36	51	M	SR	44	+	+	15	+	+	+	–	+	60	185	125
37	44	M	SR	57	–	–	0	–	–	+	–	+	65	245	180
38	57	F	PM	72	–	+	18	–	+	*	–	–	75	155	80
39	63	M	SR	57	–	+	?	0	0	+	–	+	100	250	150
40	23	M	SR	45	+	+	13	–	+	–	–	–	80	180	100
41	19	M	SR	54	–	+	1	–	+	+	–	+	80	245	165
42	52	M	SR	73	+	+	13	–	–	–	–	–	80	215	135
43	12	M	SR	60	–	+	2	+	+	–	–	–	60	165	105
44	43	F	SR	60	+	+	13	–	–	–	–	–	90	140	50
45	54	F	AF	52	+	+	7	+	+	+	–	+	65	180	115
46	46	M	SR	51	–	+	4	–	+	+	–	+	110	240	130
47	60	M	SR	63	?	?	?	0	0	+	–	–	90	180	90
48	23	F	SR	64	–	–	4	–	–	–	–	–	85	210	125
49	50	M	SR	76	+	–	5	–	–	–	–	–	100	230	140
50	34	F	SR	92	–	+	5	+	+	+	–	–	70	130	60
51	25	M	SR	73	+	–	25	+	+	+			60	120	60
52	63	M	SR	59	+	–	1	–	–	–	–	–	120	185	65
53	24	M	SR	82	+	–	12	–	–	–	–	–	65	175	110
54	59	M	AF	64	–	+	23	–	–	–	–	–	50	105	45
55	16	F	SR	69	–	–	0	–	–	–	–	–	65	135	70
56	43	M	SR	76	+	–	1	–	–	–	–	–	80	165	85
57	44	M	SR	77	+	?	?	–	+	–	–	–	50	120	70
58	62	M	SR	71	–	+	12	+	+	+	–	+	55	160	105
59	17	F	SR	80	+	+	4	–	–	+	–	+	50	150	100

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Table 1. Data in 84 Patients (*continued*)

Case	Age (yr)	Sex	Rhythm	Heart Rate	Main Symptoms		Duration (yr) of Symptoms	Pressure Gradient		SAM	Reversed Splitting	Midsystolic Closure	A_2-MO (ms)	A_2-O (ms)	MO-O (ms)
					Angina	Dyspnea		At Rest	On Provocation						
60	41	F	SR	100	−	−	0	+	+	+	−	?	100	135	35
61	26	F	SR	73	+	+	11	−	−	−	−	−	80	160	80
62	66	M	SR	61	−	−	0	+	+	+	−	+	75	165	90
63	56	F	SR	61	−	+	20	−	−	−	−	−	110	200	90
64	31	M	SR	72			0	+	+	−	−	−	85	215	130
65	11	F	SR	82	−	−	0	+	+	+	−	+	80	115	35
66	61	F	SR	69	+	+	8	+	+	−	−	−	120	225	105
67	21	F	SR	61	−	+	1	−	−	−	−	−	95	230	135
68	48	M	SR	69	+	+	5	−	+	−	−	−	105	230	125
69	47	F	SR	92	?	?	?	0	0	+	−	−	65	—	—
70	55	M	SR	56	−	+	18	+	+	+	+	+	40	130	90
71	23	M	SR	58	−	+	5	0	0	+	+	+	40	140	100
72	13	M	SR	89	−	+	10	−	+	+	+	+	35	130	95
73	36	F	SR	64	−	−	9	−	+	+	+	+	30	125	95
74	42	M	SR	56	−	−	12	−	+	+	+	+	35	190	165
75	26	F	SR	69	−	+	1	+	+	+	+	+	30	150	120
76	61	F	SR	90	+	+	1	+	+	+	+	+	10	110	100
77	59	F	SR	74	+	+	16	+	+	+	+	+	20	140	120
78	51	F	SR	78	+	+	11	−	+	+	+	+	5	115	110
79	71	F	SR	72	−	−	7	−	+	+	+	+	0	110	110
80	26	F	SR	84	+	+	4	+	+	+	+	+	0	80	80
81	54	M	SR	64	−	+	9	+	+	+	−	−	40	140	100
82	67	M	SR	64	+	−	6	0	0	+	+	+	10	80	70
83	73	F	SR	74	+	+	16	+	+	+	+	?	30	120	90
84	51	M	SR	66	+	+	8	+	+	+	+	+	35	—	—

*Prosthetic valve AF = atrial fibrillation, A_2-MO = aortic closure sound to mitral valve opening, A_2-O = aortic closure sound to O point of the apexcardiogram, MO-O = mitral valve opening to O point of the apexcardiogram, SAM = systolic anterior motion of the mitral valve, SR = sinus rhythm PM = pacemaker, 0 = no catheterization performed, ? = data unknown

as well as the instantaneously derived left ventricular dimension (Fig 3) From these tracings, the following measurements were made·

1) The time interval from minimal left ventricular dimension to aortic component of second heart sound (A_2)

2) The time interval from minimal left ventricular dimension to the onset of mitral valve opening Because these two events are almost synchronous in normal subjects, this interval represents a delay in mitral valve opening (6,23) This delay from minimal left ventricular dimension to the onset of mitral valve opening might also be due to more rapid contraction

Statistical analysis. All results of this study were reported as the mean value ± 1 standard deviation The statistical significance of differences between group means was assessed by Student's *t* test

Results

Noninvasive Data

A_2-MO (isovolumic relaxation period). In normal volunteers the period of isovolumic relaxation was 63 ± 11 ms (range 40 to 80) In the 84 patients with hypertrophic cardiomyopathy, it had a wide range of values from 0 to 160 ms (mean 71 ± 32) (Fig 4) Although the mean value of the 84 patients with hypertrophic cardiomyopathy was not significantly different from that of the normal subjects, 31 patients had an A_2-MO interval greater than 2 standard deviations above that of the normal subjects in keeping with previous reports of prolonged isovolumic relaxation in this disease However, in 15 patients, the value of this interval was smaller than 2 standard deviations below that of the normal group Figure 5 shows two patients representative of this latter group with the abbreviated A_2-MO interval In both, there is a marked delay in aortic closure causing reversed splitting of the second heart sound The aortic closure sound and mitral opening are nearly coincident, resulting in a very short A_2-MO interval

Patients with an abbreviated A_2-MO interval (Cases 70 to 84, Table 1) All 15 patients with an abbreviated A_2-MO interval had a significant gradient demonstrated during cardiac catheterization either at rest or with provocation The echocardiogram showed systolic anterior motion of the mitral valve in every patient (Fig 5) In addition, midsystolic closure of the aortic valve was demonstrated in 13 of the 15 patients and the phonocardiogram documented re-

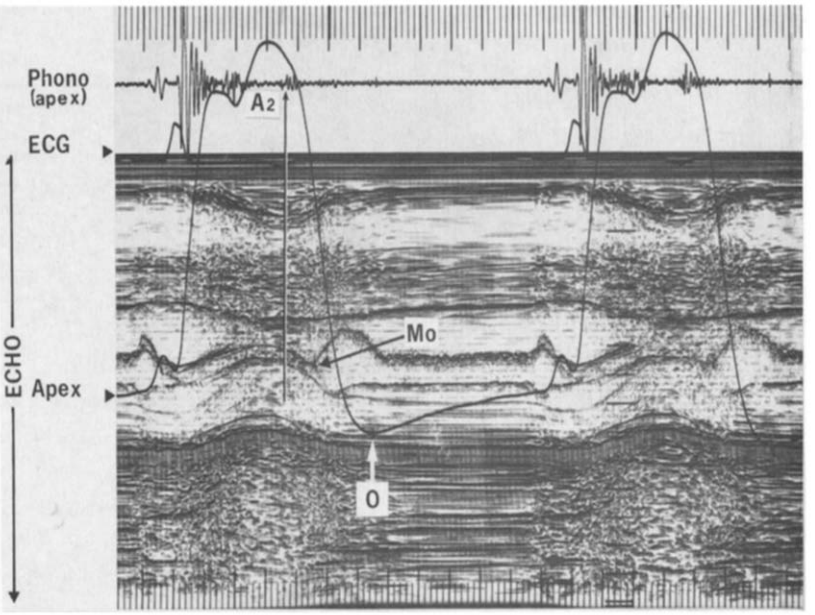


Figure 1. Case 7 Simultaneous recording of the phonocardiogram (Phono), apexcardiogram (apex) and echocardiogram (echo) with the electrocardiogram (ECG) The isovolumic relaxation period is measured from the first high frequency vibration of the aortic component of the second heart sound (A_2) to the initial separation of the two leaflets of the mitral valve (mitral valve opening, Mo) O = O point of the apexcardiogram

versed splitting of the second heart sound in 14 (Fig 2)

Further analysis of Table 1 shows that a gradient at rest or with provocation, systolic anterior motion of the mitral valve and midsystolic closure of the aortic valve were also frequently present in the first 69 patients with an A_2-MO interval greater than 41 ms. However, reversed splitting of the second heart sound was found in only one of these patients (Patient 26, with an interval of only 45 ms) Thus, reversed splitting of the second heart sound was a finding essentially specific for the patients with an A_2-MO interval less than 41 ms, suggesting that these 15 patients may represent a unique subset For this reason, the diastolic time intervals shown in Figure 6 have been analyzed separately for this subset and the remaining 69 patients with an A_2-MO interval greater than 41 ms as well as for the total 84 patients with hypertrophic cardiomyopathy When these 15 patients were excluded from the total group, the A_2-MO interval of the remaining 69 patients was significantly longer than that of the normal subjects (81 ± 24 versus 63 ± 11 ms, probability [p] < 0 001) (Fig 6)

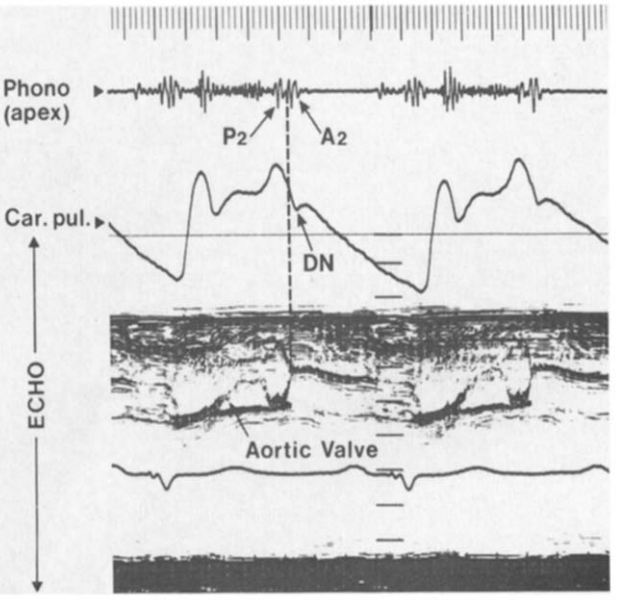
A_2-O interval. This noninvasive index was 169 ± 44 ms in the 84 patients with hypertrophic cardiomyopathy and was significantly different from that of the 31 normal subjects (130 ± 15 ms, p < 0 001) When the 15 patients with the short A_2-MO interval were excluded from analysis, there was a further increase in this interval to 178 ± 42 ms, which was markedly increased over that of the normal subjects (p < 0 001) (Fig 6)

MO-O interval. There was a significant increase in this interval (97 ± 32 ms, p < 0 001) for all 84 patients compared with that of normal volunteers (67 ± 14 ms) When analyzed separately, patients with a short and those with a prolonged A_2-MO had an increased MO-O interval compared with the values in normal volunteers (p < 0 001), but the values in the two patient groups did not differ significantly (Fig 6)

Digitized Data

Minimal left ventricular dimension–A_2 interval. In the 11 normal volunteers, aortic valve closure invariably preceded the minimal left ventricular dimension by a mean

Figure 2. Case 78 Simultaneous recording of the phonocardiogram, carotid pulse (car pul) and aortic echocardiogram with a short A_2-mitral valve opening interval Note reversed splitting of the second heart sound and partial midsystolic closure of the aortic valve The dicrotic notch (DN) of the carotid pulse and the aortic valve closure on echocardiogram confirm the last component of the second heart sound as A_2 P_2 = pulmonary component of the second heart sound, other abbreviations as in Figure 1



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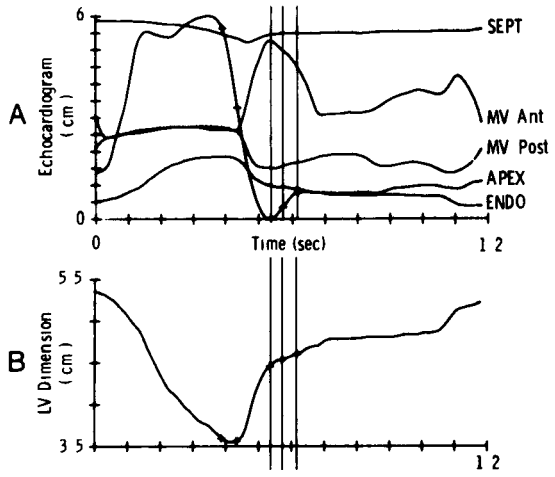
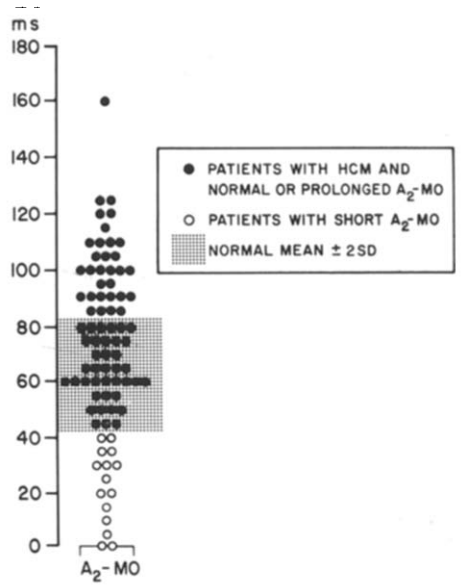


Figure 3. Computer printout showing (**A**) the left side of the septum (SEPT), posterior endocardium of the left ventricle (ENDO), anterior (MV Ant) and posterior (MV Post) mitral valve leaflet and the apexcardiogram (APEX) **B,** Instantaneous left ventricular (LV) dimension The **small crosses** on the tracing mark aortic valve closure, mitral valve opening, O point of the apexcardiogram, location of a physiologic S_3 and the F point of the apexcardiogram Minimal left ventricular dimension occurs just before mitral valve opening and no significant dimension change occurs during this brief interval

of 39 ± 18 ms, so that there was a further slight reduction in dimension during the isovolumic relaxation period In contrast, in patients with hypertrophic cardiomyopathy, this interval showed a wide range (− 100 to + 85 ms) (Fig 7) Although the range of values was large, aortic valve closure

Figure 4. The isovolumic relaxation period (aortic component of second heart sound to mitral valve opening, A_2-MO) in 84 patients with hypertrophic cardiomyopathy (HCM) Fifteen patients (**open circles**) have an A_2-MO interval smaller than 2 standard deviations below that of the 31 normal volunteers (63 ± 22 ms)



followed the minimal left ventricular dimension by a mean of 9 ± 39 ms, which was significantly different from that of the normal group ($p < 0.001$) In the group of patients with the shortened isovolumic relaxation period, there was a further delay in aortic valve closure, which followed the minimal left ventricular dimension by a mean of 31 ± 30 ms (Fig 7)

Minimal left ventricular dimension–MO interval. The onset of opening of the mitral valve was appreciably delayed by a mean value of 79 ± 38 ms in relation to the time of minimal cavity dimension when the whole group of patients was considered, and this was significantly above the mean of the normal values ($p < 0.001$) Figure 7 shows the distribution of this delay in onset of mitral valve opening in relation to minimal cavity dimension The delay in patients with a shortened isovolumic relaxation period had a mean value of 53 ± 33 ms and was significantly below that of the remaining 61 patients ($p < 0.025$), but was also significantly above the mean value of the normal subjects (25 ± 15 ms, $p < 0.025$) (Fig 6) In addition to the delayed onset of mitral valve opening relative to minimal dimension in patients with hypertrophic cardiomyopathy, an abnormal increase in ventricular dimension before mitral valve opening was common, the mean value being 24 ± 13% of the total diastolic increase compared with 4 ± 3% in normal subjects ($p < 0.001$)

Discussion

Isovolumic relaxation period in normal subjects. In the 31 normal subjects studied, the mean value of the isovolumic relaxation period was 63 ms with a standard deviation of ± 11 ms This value is almost identical to that recently reported by Chen and Gibson (25) (65 ± 15 ms), using an identical technique When the aortic component of the second heart sound is used as the noninvasive marker for the beginning of the isovolumic relaxation period and the initial separation of the mitral leaflets as the termination of this interval, its duration is determined not only by the rate of relaxation of the left ventricle, but also by the magnitude of the pressure drop (12,26,27)

This relation can best be understood by considering the isovolumic relaxation period as the base of a right triangle, the height of which is the difference between the left ventricular pressure at the time of the aortic incisura (A_2) and the pressure at the time of the left ventricular left atrial crossover (mitral valve opening) and the slope of which is the rate of decline of left ventricular pressure It is important to appreciate that the duration of this interval is multifactorially determined and that its reproducibility and small standard deviation in the normal subjects is a reflection of normal left ventricular relaxation in subjects with normal arterial blood pressure and normal left ventricular filling pressures.

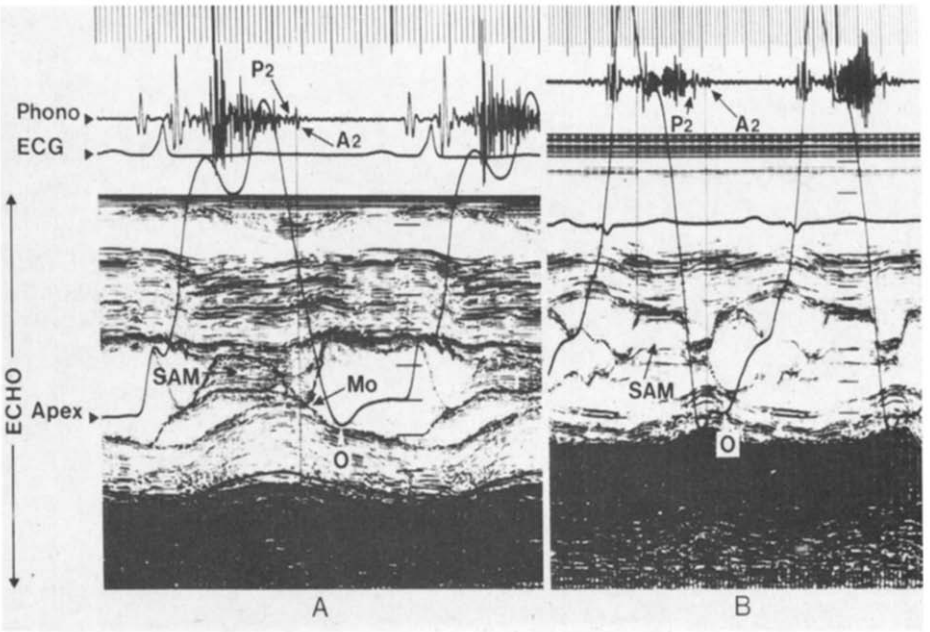


Figure 5. Cases 75 (**A**) and 78 (**B**). Simultaneous recordings of the phonocardiogram, apexcardiogram, electrocardiogram and echocardiogram in two patients with hypertrophic cardiomyopathy having a short isovolumic relaxation period. Systolic anterior motion (SAM) of the mitral valve is present in both as well as marked delay in A_2 with reversed splitting of the second heart sound. The initial separation of the anterior and posterior mitral leaflets occurs shortly after A_2, resulting in a very abbreviated A_2-mitral valve opening interval. A loud systolic murmur is present in both patients. Abbreviations as before.

Isovolumic relaxation period in patients with hypertrophic cardiomyopathy. When the A_2-MO interval in the 84 patients with hypertrophic cardiomyopathy was compared with this interval in the normal volunteers, there was no significant difference (71 ± 32 versus 63 ± 11 ms). However, the range of this interval in this large patient group

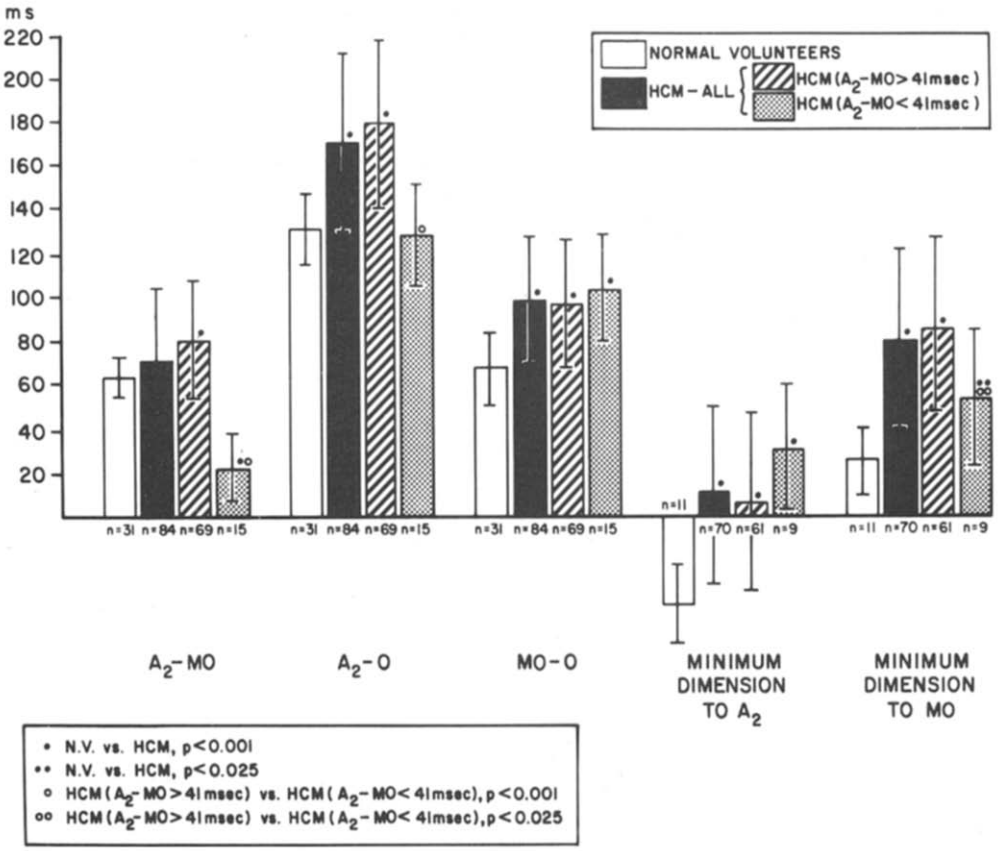


Figure 6. Diastolic time intervals in patients with hypertrophic cardiomyopathy (HCM) and normal volunteers (N.V.). Patients with cardiomyopathy with an A_2-mitral valve opening interval (A_2-MO) greater than and less than 41 ms are compared with normal volunteers and each other. Abbreviations as before.

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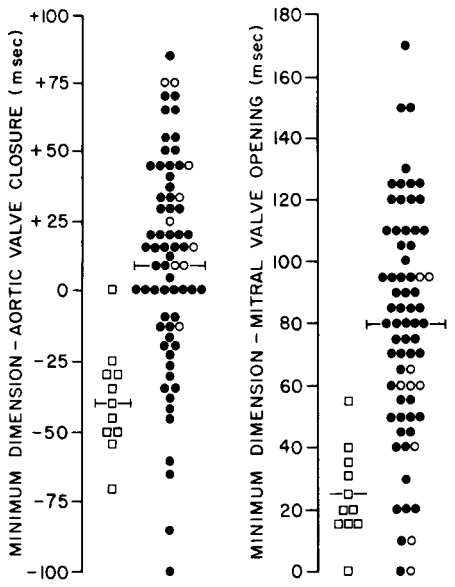

Figure 7. Time to aortic valve closure (**left**) and mitral valve opening (**right**) with respect to minimal left ventricular dimension in 11 normal volunteers (**squares**) and in 70 patients with hypertrophic cardiomyopathy with normal or prolonged (**closed circles**) or short (**open circles**) A_2-mitral valve opening interval

varied between 0 and 160 ms, and there were 15 patients in whom the value of this interval was below 2 standard deviation of the normal range Fourteen of the 15 patients in this subset had marked delay in the aortic closure sound, producing reversed splitting of the second heart sound, while only 1 of 69 patients with an A_2-MO interval greater than 41 ms had this finding, suggesting that this group might represent a unique subset When the remaining 69 patients were then compared with the normal subjects, there was a highly significant increase in the A_2-MO interval This mean value of 81 ± 24 ms is very similar to the value recently reported by Hanrath et al (6) (92 ± 10 ms) in a study in which a much smaller group of patients was analyzed Likewise, when the A_2-O interval in these 69 patients was compared with that in normal subjects, there was a significant increase with a mean value comparable with values found in previous studies of hypertrophic cardiomyopathy The data in these 69 patients would then be consistent with earlier studies (7,8,13–15) confirming a significant prolongation of either index of left ventricular relaxation in primary myocardial hypertrophy Although it is tempting to attribute this abnormal relaxation to the altered anatomic architecture in hypertrophic cardiomyopathies, recent studies by Gibson et al (5) have shown that the physiologic effects of severe left ventricular hypertrophy on diastolic function are identical whether the hypertrophy is primary or secondary

Mechanism of extremely short A_2-MO interval. The short A_2-MO interval found in the 15 patients with hypertrophic cardiomyopathy is readily explained by hemodynamic data obtained at cardiac catheterization In Figure 8, the left ventricular, aortic and left atrial pressures are recorded with a Millar catheter-tip micromanometer during diagnostic catheterization in a 71 year old woman with a dynamic left ventricular outflow tract pressure gradient On noninvasive evaluation a few days before catheterization (Fig 9), the patient had reversed splitting of the second heart sound, systolic anterior motion of the mitral valve and partial preclosure of the aortic valve with an isovolumic relaxation period (A_2-MO interval) of 0 ms

In the left panel of Figure 8, there is significant prolongation of the left ventricular ejection time as a result of a large pressure gradient, thereby markedly delaying A_2. In this condition, A_2 is a poor marker of the onset of active left ventricular pressure decline which has begun well before this event In the next panel, recorded at a different time during the procedure, only a minimal pressure gradient is present, splitting is normal and the level of the aortic incisura is considerably higher The aortic component of the second heart sound (A_2) is now a more appropriate marker of the onset of left ventricular pressure decline and the A_2-MO interval is increased compared with the previous panel In the third panel, equisensitive left ventricular and left atrial pressures are displayed, showing pressure crossover at 23 mm Hg with an A_2 to pressure crossover (mitral valve opening) interval of 50 ms In the next panel, after the left ventricular angiogram, there is a marked increase in the height of the left atrial V wave and the pressure crossover and A_2 are coincident, giving an A_2-MO interval of 0 ms

Thus, the duration of the A_2-MO interval is constantly changing, depending on the magnitude of the pressure gradient delaying A_2 and the level of the left atrial pressure. Two additional patients with a short isovolumic relaxation period were studied with catheter-tip micromanometers, showing similar delays in A_2 resulting in abbreviated A_2-MO interval

These data clearly show that it is the delayed aortic closure that is primarily responsible for the short A_2-MO interval and, in this situation, A_2 is a poor marker of the onset of relaxation, occurring well down the descending limb of the left ventricular pressure curve All 15 patients in this subset with a short A_2-MO interval had a significant outflow tract gradient either at rest or with provocation, as well as systolic anterior motion of the mitral valve In addition, 13 of the 15 patients also had midsystolic closure of the aortic valve However, many other patients with a similar outflow gradient and echocardiographic findings had a normal or prolonged A_2-MO interval (Table 1) It is only in those patients who had reversed splitting with a marked delay in A_2 that there was a short A_2-MO interval This marked prolongation of left ventricular ejection time producing reversed splitting is most likely a result of the combination of prolongation of both the contraction and relaxation phases In this subset of patients, then, the abbreviated A_2-MO interval is not a valid measurement of left ventricular

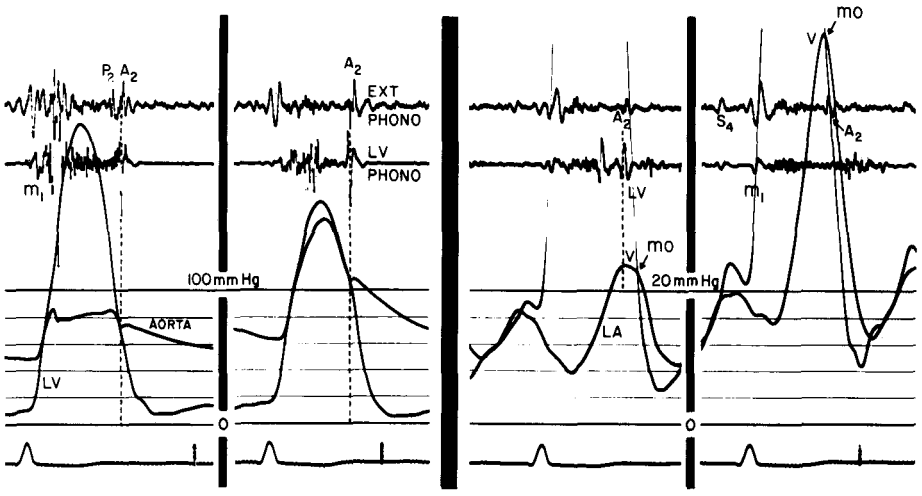

Figure 8. Case 79. Simultaneous left ventricular (LV), aortic and left atrial (LA) pressure recorded from high fidelity catheter-tip micromanometers (Millar) together with the external phonocardiogram (EXT PHONO) and the left ventricular phonocardiogram (LV PHONO) and the electrocardiogram. In the **left two panels,** equisensitive left ventricular and aortic pressures are recorded on a 0 to 100 mm Hg scale. In the **right two panels,** equisensitive left ventricular and left atrial pressures are recorded on a 0 to 20 mm Hg scale. In the two right panels, isovolumic relaxation period is the interval between A_2 and mitral valve opening (mo) at left ventricular (LV) and left atrial (LA) pressure crossover (**arrow**). See text for details. m_1 = mitral component of the first heart sound; V = V wave.

relaxation. This inability of A_2 to accurately estimate the onset of rapid left ventricular pressure decline is a major limitation of this noninvasive technique.

Delay in aortic closure relative to minimal dimension. Consistent with this hemodynamic explanation is the marked delay in aortic closure relative to minimal dimension (Fig. 7). In the normal subjects whose ventricular relaxation is a highly organized process, precisely timed and sequenced, A_2 always precedes minimal dimension (39 ± 18 ms), which in turn is shortly followed by mitral valve opening (25 ± 15 ms) (7,23,28). In the 70 patients, however, the mean value of aortic closure was significantly delayed, occurring 9 ± 39 ms after minimal dimension. In the nine patients with reversed splitting and a short A_2-MO interval, A_2 followed minimal dimension by a mean value of 31 ms thereby considerably encroaching on the true period of left ventricular pressure decline.

Interval of minimal dimension to mitral valve opening. When this interval is compared with the value in normal subjects, there is a marked increase when all 70 patients are considered (79 ± 38 versus 25 ± 15 ms, $p < 0.001$) as well as when only those with a short A_2-MO interval are considered (59 ± 33 versus 25 ± 15 ms, $p < 0.025$). Our mean value of 79 ± 38 ms for all 70 patients is similar to

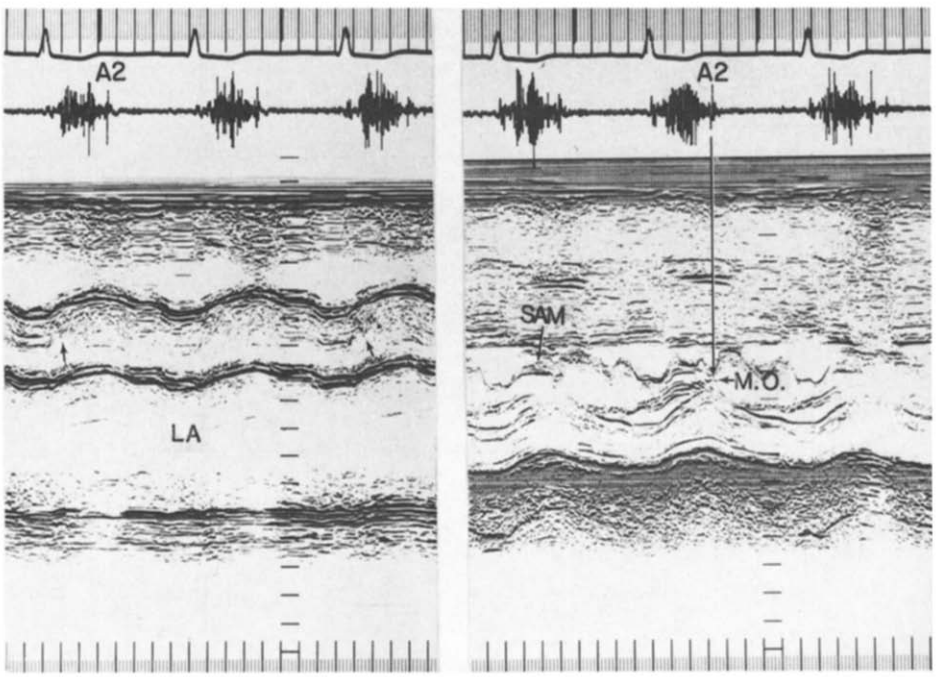

Figure 9. Case 79. Simultaneous recordings of the phonocardiogram, electrocardiogram and echocardiogram. On the **left panel,** note partial preclosure of the aortic valve (**arrows**). On the **right panel,** A_2 and mitral valve opening (M.O.) are coincident, resulting in an isovolumic relaxation period of 0 ms. A loud systolic murmur is associated with systolic anterior motion (SAM) of the mitral valve. LA = left atrium.

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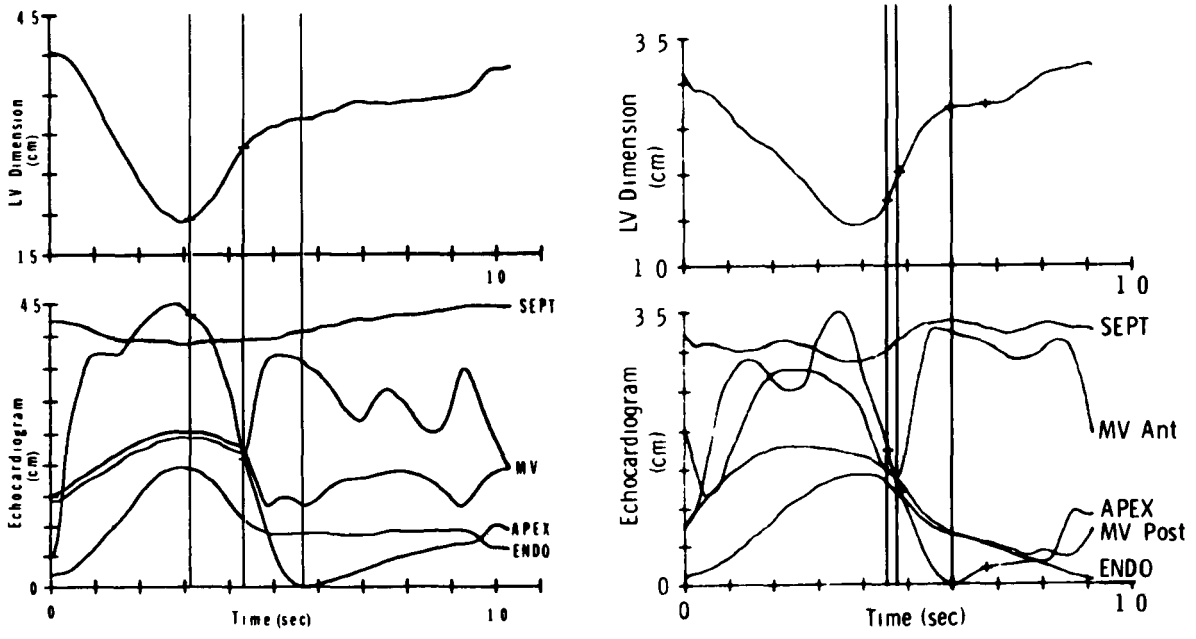
the mean value of 75 ms recently reported by Gibson et al (5), and (93 ± 37 ms) Hanrath et al (6) In both of these studies, the minimal dimension to mitral valve opening was used as the noninvasive index of the isovolumic relaxation period However, it should be noted that both in our study and in the study by Hanrath et al there is a large standard deviation with a wide range of values This most likely is the result of the computer's inability to accurately and reproducibly identify minimal dimension when septal motion is almost flat In this situation, minimal dimension is not a discrete point and, as such, is a limitation of this noninvasive technique

In Figure 10, the computer printout of the course of relaxation is shown in a typical patient with a prolonged A_2-MO interval and one with a short A_2-MO interval In both, the sequence of diastolic events is markedly altered compared with that in normal subjects (Fig 3) In each case, A_2 is delayed relative to minimal dimension In the left panel, both the A_2-MO interval and the minimal dimension to mitral valve opening are increased In the right panel, due to the marked delay in A_2, the A_2-MO interval is decreased while minimal dimension to mitral valve opening remains prolonged compared with that in normal subjects As previously mentioned, earlier mitral valve opening secondary to high left ventricular-left atrial pressure crossover may occur, further decreasing the A_2-MO interval This earlier pressure crossover may also be responsible for the shorter minimal dimension to mitral opening found in the subset of patients with a short A_2-MO interval (53 ± 33 ms) compared with that in the remaining patients with hypertrophic cardiomyopathy (84 ± 37 ms, $p < 0.025$) It would not be unexpected for patients with an outflow pressure gradient to have higher filling pressures and greater degrees of mitral regurgitation This earlier opening of the mitral valve in this subset may also be responsible for the observed increased trend in the MO-O interval in this group

As can be seen in Figure 10, significant changes in diastolic dimension occur in both patients with hypertrophic cardiomyopathy before the mitral valve opens and should be contrasted with Figure 3 where only a minimal change occurs in the normal volunteers In our study, a mean change of 24% in diastolic dimension occurred before mitral valve opening and is very similar to the 28% change reported by Gibson et al (5) in 30 patients with hypertrophic cardiomyopathy studied by the same technique Similar shape changes during isovolumic relaxation have also been confirmed by other investigators (6)

Conclusions. The results of this large study of 84 patients support previous findings demonstrating significant abnormalities in diastolic relaxation in patients with hypertrophic cardiomyopathy Both the timing and sequence of relaxation are altered, as is the rate of relaxation Although a subset of patients with hypertrophic cardiomyopathy has been identified with a very short isovolumic relaxation period and reversed splitting of the second heart sound, careful scrutiny of this subset with hemodynamic evaluation has

Figure 10. Cases 7 (**left**) and 75 (**right**) Computer printout of two patients with hypertrophic cardiomyopathy, one with a prolonged (Case 7), and the other (Case 75) with a short isovolumic relaxation period In both patients, A_2 follows minimal left ventricular (LV) dimension and a significant increase in dimension occurs before the mitral valve (MV) opens In both patients, mitral valve opening is markedly delayed relative to minimal dimension The **vertical lines** represent aortic closure, mitral valve opening and the O point of the apexcardiogram Abbreviations as in Figure 3



shown that this noninvasive interval may not always be a valid measure of left ventricular relaxation When the A_2 mitral opening interval is used to evaluate left ventricular relaxation, the right triangle relation of the magnitude of pressure decline and its slope as well as the appropriateness of A_2 as a marker of the onset of relaxation must be kept in mind

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